

## **HIV-1 CD4 binding site antibody N49P6 mimics CD4 in its quaternary interactions with the HIV-1 Envelope trimer.**

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The first step in the HIV-1 entry process is the attachment of the Envelope (Env) trimer to target cell CD4. As such, the CD4 binding site (CD4bs) remains one of the only universally accessible sites on the Env trimer. Few antibodies (Abs) are able to capitalize on this however, due the steric constraints involved in accessing the CD4bs. We recently characterized a near pan neutralizing Ab isolated from the plasma of a HIV-1 "elite neutralizer", N49P7. N49P7 combines many characteristic CD4bs Ab features along with unique interactions to the highly conserved gp120 inner domain Layer 3 to achieve its remarkable neutralization breadth and potency. Here we characterize the Ab N49P6 from the same donor and show that N49P6 utilizes many of these characteristics to achieve similar breadth. Further, we determined the structure of N49P6 in complex with BG505 SOSIP and show that N49P6 mimics CD4 in its initial quaternary contacts with the neighboring gp120 in the trimer. The details of these interactions pave the way to the creation of the next generation of HIV-1 neutralizing Abs for the use in preformed vaccines and HIV-1 therapeutics.